REMARKS

This Amendment and Remarks are filed in response to the Office Action dated June 12, 2006 wherein claims 12-15 and claims 21-33 are rejected.

Election/Restrictions

Examiner acknowledges Applicant's election of Group III (claims 12-15) with traverse in the reply filed on December 7, 2005.

The Examiner notes that the Applicant failed to address the generic species elections of a composition form (i.e., powders or aerosolizable solutions) and a specific gram-negative bacteria, originally stated in claims 1 and 3, respectively.

The requirement is still deemed proper and is therefore made Final.

Applicants apologize for oversight in making this election and elect to prosecute powders species as a composition form and *Burkholderia cepacia* species as a gram-negative bacteria.

Specification

Examiner objects to the incorporation of essential material in the specification by reference to an unpublished U.S application, foreign application or patent, or to a publication as being improper and requires Applicant to amend the disclosure to include the material incorporated by reference, if the material is relied upon to overcome any objection, rejection, or other requirement imposed by the Office. The amendment must be accompanied by a statement executed by the applicant, or a pract6itioner representing the applicant, stating that the material being inserted is the material previously incorporated by reference and that the amendment contains no new matter.

Applicants incorporation by reference concerns only the issued U.S. patents or published applications permitted under MPEP 608.01 (p).

The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

Currently, Applicants discovered only one minor typographical error, corrected by amendment submitted herein.

Claim 12 is objected to because of the following informalities: the Examiner believes the word "to" in line 7, should be replaced by the word "of". Appropriate correction is required.

Applicants disagree, however, Applicants respectfully submit that in view of the newly amended claim 12, the objection is moot.

Rejections under 35 USC § 112

Claims 27 and 28 are rejected under 35 USC 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention.

The term "substantially" in claim 27 is a relative term, which renders the claim indefinite. The term "substantially" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprized of the scope of the invention. A person of ordinary skill in the art at the time of the instant invention would be unable to ascertain what Applicant considers the appropriate meaning of the phrase: "substantially free of an ethyl ester contaminant".

Applicants disagree, however, to overcome Examiners rejections, Applicants amended claim 27 to make it more definite.

The term "reduced" in claim 28 is a relative term, which renders the claim indefinite.

The term "reduced" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonable apprized of the scope of the invention. A person of ordinary skill in the art would not be able to ascertain what Applicant considers "reduced" quantity of beta lactams ring contaminant.

Applicants disagree, however, to meet Examiners rejections, Applicants canceled claim 28.

Rejections under 35 USC § 103

This application currently names joint inventions. In considering patentability of the claims under 35 USC 103(a), the Examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 USC 103(c) and potential 35 USC 102(e), (f) or (g) prior art under 35 USC 103(a).

Applicants confirm that inventorship of the amended claims remain the same.

Claims 12-15 and 21-33 are rejected under 35 USC 103(a) as being unpatentable over Kuo et al. (U.S. Patent No. 6,518,239) in view of Bastin, R.J. ("Salt Selection and Optimization Procedures

for Pharmaceutical New Chemical Entities" Org. Proc. Res. & Develop., 4:427-435 (2000).

The pending claims of the instant application are product-by-process claims and are therefore treated as compositions. Procedural steps, which have no effect on the make up of the composition, are given no weight in this examination (e.g. administration).

Applicants disagree. The current claims are composition claims directed to a specific aztreonam salt, namely aztreonam lysinate salt, and particularly to the alpha aztreonam lysinate, that was previously not known and used for treatment of gram-negative bacteria by aerosolization. Newly amended claims are not the product-by process claims.

Examiner argues that Kuo teaches highly dispersible formulations comprising an active agent and peptides, wherein the compositions exhibit superior aerosol properties and are preferred for aerosolized administration to the lung, (i.e., inhalation) (Abstract).

Applicants disagree that Kuo's reference makes the current claims obvious. Kuo' dry powder dispersable compositions comprise an active agent and, mandatorily, a very defined dispersibility enhancing peptide, namely di- or tri-peptide comprising at least two leucyl residues.

The current invention and claims do not combine aztreonam lysinate salt with any peptide, not the least such specifically defined peptide, or with any other compound. The current composition comprises a compound that has never before been prepared, used or approved for inhalation purposes and used for treatment of gram-negative bacteria. Novelty and non-obviousness of the current composition rests with identification of a specific

compound (aztreonam lysinate salt) that, when prepared in a form of particle sizes suitable for pulmonary administration(1-5μ) and diluted with normal or half or quarter normal saline (without the presence of any other compounds, enhancer or additives) and administered in an aerosol according to the invention has an antibacterial activity against resistant gram-negative bacteria. These bacteria were, until today, difficult, if not impossible, to treat as they do not respond to commonly used antibiotics.

Examiner argues that Kuo teaches that the dry powders of the invention are characterized by both physical and chemical stability upon storage. In one embodiment, the chemical stability of the dry powder is characterized by degradation of less that about 5% by weight of the active agent upon storage of the dry powdered composition under ambient conditions for a period of three months.

Applicants disagree that Kuo's claims of stability of his powders makes the current claims obvious. As pointed out above, the current invention and claims concerns solely the aztreonam lysinate powder having particle sizes between 1 and 5μ. The aztreonam lysinate powder prepared from the alpha aztreonam is stable for 3 months with degradation of only 1.2%. Such stability is achieved despite of the fact that no additional agents are added to enhance the stability of the aztreonam lysinate.

Examiner further argues that Kuo teaches highly desirable dry powder formulations comprising an active agent, wherein the preferred active agents include, for example, respiratory drugs; anti-infectives (e.g. antibiotics), gram negative microorganism active agents (e.g. ampicillin), monobactams, such as aztreonam, and the acceptable salts may include phosphate, chloride, lactate, stearate, etc. The active agent is delivered in doses from about 0.001 mg/day to 100 mg/day. The term "aztreonam" encompasses all

forms of aztreonam such as the alpha and beta forms.

Applicants would not know if the Kuo's dry powder formulation is highly desirable or not, however, regardless of such desirability they disagree that Kuo reference makes the aztreonam lysinate salt composition of the invention obvious. First, Kuo never mentions aztreonam lysinate or any other aztreonam salt as a possible active compound. Second, he lists monobactams, such as aztreonam, as compounds that would be deliverable as dispersable dry powders when combined with the dispersibility enhancing peptides, as described by Kuo. Even if formulated according to Kuo's invention, the resulting composition would be the aztreonam in combination with the di- or tripeptide comprising at least two leucyl groups. To the contrary, the current invention does not utilize any additional compounds, be it peptides or other compounds, for the aztreonam lysinate powder composition. As pointed out above, the current invention and claims concerns solely the aztreonam lysinate powder having particle sizes between 1 and 5 μ.

Examiner is also mistaken in arguing that the aztreonam Kuo is disclosing encompasses all forms of aztreonam and all salts. How could he disclose compounds, their salts and isomers when such forms were not known to exist and be stable. Kuo could not enable compounds he did not know existed.

Examiner also argues that Kuo teaches that the therapeutically effective amount of active agent in the formulations will vary widely depending on the particular agent, its activity, the severity of the condition to be treated, the patient population, dosing requirements, and the desired therapeutic effect.

Applicants again disagree with Examiner's arguments. Effective amount of the aztreonam lysinate for aerosolized treatment of gram-

negative bacteria, namely 1 to about 250 mg/one dose, was never before disclosed or determined. Kuo's reference discloses a common knowledge for activity of the pharmaceutically active compounds found in many other references. Such common knowledge does not make the current claims obvious.

Examiner argues that Kuo teaches that more than one active agent may be incorporated into the formulations.

Applicants agree that Kuo may possibly add more than one active agent to his composition. To applicants best knowledge, however, the current claims do not claim any combination of other drugs with the aztreonam lysinate salt.

Examiner cites the Example 1 (Tables 1-4) as showing a pH range from about 4.0 to about 10.0 and Kuo teaches the compositions may comprise a pH adjusting agent or a buffer. The formulations may be in a dry powder or liquid form (i.e. solutions or colloidal suspensions). The active agent can be dissolved in a solvent (water, ethanol, ethanol-water, saline). The dry powder formulations can be made by lyophilization, spray drug, spray freeze-drying, etc. The devices suitable for delivery of said formulations are discussed in columns 14-15. The said devices include dry powder inhalers, metered dose inhalers, and nebulizers. It is also disclosed that alternatively, the powders may be dissolved or suspended in a solvent such as water, ethanol, or saline and administered by nebulization.

Applicants again disagree. As discussed above, the current claims are directed solely to the compound that has hence before not been known to exist in a stable form, particularly where it concerns alpha aztreonam lysinate and the salt of which was not known to be used for aerosolized treatment of gram-negative bacteria. Moreover, the lysinate salt of the invention is

dissolved in normal or diluted half or quarter normal saline or solution of corresponding strength and is administered to the lungs at a physiologically acceptable pH between pH 4,2 and 7.5. Applicants respectfully submit that the pH between 4 and 10, as Examiner states, disclosed by Kuo for aerosolized delivery of his compositions causes broncho-constriction, cough, inflammation, irritation and other complications.

Examiner himself admits that Kuo lacks the teaching of a lysine salt form of aztreonam and that is really the crux of the rejection here. Kuo describes the composition for aerosolization where he list all possible drugs without enabling majority of them or providing any evidence that many of his formulation would work and particularly not the composition formulated without mandatory added dispersibility enhancing peptides. Examiner is trying to circumvent this deficiency in his rejections by combining the Kuo reference with the teachings of Bastin's reference, Purification of Laboratory Chemicals (PLC, 4th Edn., Elsevier: 1996, Chapter 1, provided herein to demonstrate what was well known in the art regarding the physical purification of organic compounds.

Examiner provides and exhaustive list of PLC teachings that, he argues would make this invention obvious by, for example, arguing that by suitable manipulation it is often possible to reduce the levels of impurities to acceptable limits, but absolute purity is an ideal, which, no matter how closely approached, can never be attained. Further, according to the Examiner, PLC teaches that if a solution contains extraneous colored material it is likely to contaminate the desired product, this can often be removed by adding some activated charcoal (decolorizing carbon) and that PLC teaches that filtration removes particulate impurities from liquids and is also used to collect insoluble or crystalline

solids, which separate or crystallize from solutions.

Examiner then argues that it would have been obvious to a person of ordinary skill in the art at the time of the instant invention to combine the teachings of Kuo and Bastin, because Kuo teaches formulations comprising aztreonam and its pharmaceutically acceptable salts.

Applicants strongly disagree with the above arguments. Kuo teaches no such thing and here again, Examiner conveniently forgets the mandatory presence of dispersibility enhancing agents in Kuo's formulation. Kuo teaches the powder or solution compositions for aerosolization of various compounds wherein such aerosolization is achieved with formulation mandatorily containing the presence of specifically defined dispersibility enhancing peptides, as already discussed above.

Examiner continues with statements that Kuo discloses an inhalable formulation comprising an active agent such as aztreonam, in either dry powder form or solution, where the dose is from 0.001 to 100 mg/day, wherein the solvent is water, ethanol, ethanol-water or saline. Regarding claims 12-15 and 22-24, Examiner states that it would have been apparent to a skilled artisan that optimization of the amounts of the different components in a particular dosage form (e.g., an aqueous solution or dry powder) would be modified depending on the severity of the infection to be treated, the patient needing treatment, etc., as taught by Kuo.

Applicants again disagree with the Examiner. Kuo cannot disclose something that he does not know exists. Applicants discovered not only that aztreonam lysinate, as such, when administered by aerosolization, is able to treat the antibiotic resistant gram-negative bacteria, such as *Burkholderia cepacia*, but also that the aztreonam, previously only available and approved

for IV administration in the form of arginine, can be formulated as a lysinate salt and that this salt is eminently effective for treatment of gram-negative bacteria otherwise unresponsive to treatment. Additionally, Applicants discovered that the isomeric form alpha aztreonam can be prepared in a stable form, the fact previously not known, and that this form of aztreonam lysinate is much more stable and pure than the form prepared from the beta form. Applicants wonder how can Examiner justify his obviousness rejections of the current invention when his rejection is based on the reference that concerns compositions comprising different compounds that mandatorily require the presence of the dispersion enhancer in order to be made suitable for aerosolization, when the cited reference is not directed to the compound claimed herein and/or to the stable isomer not known to exist at the time when the cited reference was published.

Examiner continues in arguing that the amount of a specific ingredient in a composition is clearly a result effective parameter that a person of ordinary skill in the art would routinely optimize. Optimizaton of parameters is a routine practice that would be obvious for a person of ordinary skill in the art to employ. It would have been customary for an artisan of ordinary skill to determine the optimal amount of each ingredient needed to achieve the desired results. Thus, absent some demonstration of unexpected results from the claimed parameters, the optimization of ingredient amounts would have been obvious at the time of applicants invention. Because the therapeutically effective amount of an active agent required is affected by the severity of the condition to be treated, the patient population, and the desired therapeutic effect, it would have been obvious to a skilled artisan to modify the dosing requirements in a given treatment to obtain

the best therapeutic response in a subject treated with said compostions. Finally, a skilled artisan would have had a reasonable expectation of successfully combining the teachings of Kuo and Bastin, because Kuo teaches inhalable pharmaceutical formulations comprising active agents and/or pharmaceutically acceptable salts thereof, and Bastin teaches the motivation for using salts, with lysine salts given as an example of commonly employed amino acid salt forms. It would have been apparent to a skilled artisan that Kuo's dry powder formulations are stable, because Kuo reported a degradation of less than 5% in a period of three months.

Applicants disagree that their invention constitutes optimization of known parameters. When the composition is novel insofar that it contains a never before disclosed salt of the compound, when it shows that the isomer previously known to be unstable and unsuitable (Spec. Page 18-21, section B) for any use when prepared according to the invention becomes an effective treatment for bacterial infections resistant to treatments in amounts that are shown to be therapeutic for treatment of patients in the clinical trials (see Examples 2 and 9-11), no optimization argument can be justified.

It is respectfully submitted that the current claims are not obvious over Kuo in view of Bastin. The rejection under 35 U.S.C. 103 over Kuo in combination with Bastin should be withdrawn.

Rejection under 35 U.S.C. 103

Claims 12-15 and 21-33 are rejected under 35 USC 103(a) as being unpatentable over Varia et al. (EP 0297580) in view of Bastin, R.J. ("Salt Selection and Optimisation Procedures for Pharmaceutical New Chemical Entities" Org. Proc. Res. & Develop., 4:427-435 (2000) and Akehurst (U.S Patent No. 6,303,103).

The pending claims of the instant application are product-by-process claims and are therefore treated as compositions. Procedural steps, which have no effect on the make up of the compositon, are given no weight in this examination (e.g. administration steps).

Examiner cites Varia references and argues that Varia discloses all teachings as listed below.

Varia teaches the preparation of the amorphous form of alpha- and beta- aztreonam and its pharmaceutically acceptable salts. The use of the amorphous aztreonam in pharmaceutical formulations results in products with good stability along with low particulate contamination.

Varia teaches that freeze-dried or lyophilized L-arginine aztreonam salt for injections is prepared by mixing the required amount of alpha- or beta- aztreonam and 90% of the required L-arginine together. An in-process titration of alpha-aztreonam and L-arginine is used to determine the amount of arginine required.

Varia teaches that the pH is adjusted via the addition of L-arginine to a pH value of 5.0, and the resulting solution is clarified and aseptically filtered. The resulting solution is transferred to the appropriate container and freeze-dried by conventional methods (i.e., lyophilized). The lyophilized product is reconstituted in diluent, using various volumes of diluent and quantities of aztreonam, depending on the intended use. Acceptable diluents are water, and others known to one skilled in the art.

Varia teaches that other basic materials can be mixed with crystalline aztreonam to yield the desired lyophilized aztreonam salt product for reconstitution.

Examiner admits that Varia lacks the teaching of aztreonam lysinate (i.e., the lysine salt of aztreonam), alpha-aztreonam

lysinate, and inhalable powders or aerosolizable solutions.

Examiner further cites Bastin and combines Bastin teachings with Varia as follows.

Bastin teaches that the selection of an appropriate salt form for a new chemical entity provides the pharmaceutical chemist and formulation scientist with the opportunity to modify the characteristics of the potential drug substance and to permit the development of dosage forms with good bioavailability, stability, manufacturability and patient compliance. Salts are most commonly employed for modifying aqueous solubility, however the salt form will influence a range of other properties such as melting point, hygroscopicity, chemical stability, dissolution rate, solution pH, crystal form, and mechanical properties.

Bastin teaches that drug candidates are usually free bases, free acids, or neutral molecules, rather than their salts.

Bastin teaches that for weekly basic drug substances, salts of amino acids (arginine or lysine), etc., could be considered.

Examiner further adds the Akehurst reference to this combination and argues that Akehurst teaches as follows.

Akehurst teaches aerosol formulations for the administration of medicines by inhalation, which may contain a combination of two or more active ingredients. Aerosol compositions containing two active ingredients are known for the treatment of respiratory disorders. Acceptable medicaments for use in the Akehurst's formulations include, anti-infectives, including penicillins. Akehurst also teaches that it is clear to a person of skill in the art that medicaments may be used in the form of salts (e.g., alkali metal or amine salts or as acid additions salts) or as esters or solvates to optimize activity, and/or stability, and/or to minimize solubility of the medicament in the propellant.

Examiner further combines all above references with the following Purification of Laboratory Chemicals (PLC), 4th Edn., Elsevier: Chapter 1 (1996) reference, provided to demonstrate what was well known in the art regarding the physical purification of organic compounds.

PLC teaches that by suitable manipulation it is often possible to reduce the levels of impurities to acceptable limits, but absolute purity is an ideal, which, no matter how closely approached, can never be attained.

PLC teaches that if a solution contains extraneous colored material likely to contaminate the desired product, this can often be removed by adding some activated charcoal (decolorizing carbon).

PLC teaches that filtration removes particulate impurities from liquids and is also used to collect insoluble or crystalline solids, which separate or crystallize from solution.

Examiner then concludes that it would have been obvious to a person of ordinary skill in the art at the time of the instant invention to combine the teachings of Varia, Bastin and Akehurst, because Bastin teaches the development of salt forms of a candidate drug (influencing chemical stability, solubility, solution pH, etc), including the use of lysine salts, is commonly practiced in the art and Akehurst teaches medicinal aerosol formulations comprising anti-infectives for administration by inhalation. A skilled artisan would be motivated to use a lysine salt of alpha-aztreonam in lieu of the arginine and would have a reasonable expectation of success in the use of a lysine salt in lie of an arginine salt, because lysine salts are know pharmaceutically acceptable salt forms of drug candidates. The optimization of a composition's purity by the reduction of the amount of impurities present would have been obvious to a person of ordinary skill in

the art at the time of the instant invention. Routine optimization of an alpha-aztreonam lysinate composition would have yielded a composition having minimal amounts lower that 1%. It would have been apparent to a person of ordinary skill that a reduction of the levels of impurities would also enhance the stability of a composition. It would also have been obvious to a skilled artisan to make an inhalable composition, because aerosol formulations containing two medicaments are known for the treatment of respiratory disorders (Akehurst). The amount of a specific ingredient in a composition is clearly a result effective parameter that a person of ordinary skill in the art would routinely optimize. Optimization of parameters is a routine practice that would be obvious for a person of ordinary skill in the art to employ. It would have been customary for an artisan of ordinary skill in the art to employ. It would have been customary for an artisan of ordinary skill to determine the optimal amount of each ingredient needed to achieve the desired results. Thus, absent some demonstration of unexpected results from the claimed parameters, the optimization of ingredient amounts would have been obvious at the time of applicant's invention.

Applicants disagree with Examiner's rejections based on combination of Varia, Bastin and Akehurst and further with PLC. Varia reference describes preparation of aztreonam arginine and other salts derived from α- or β-aztreonam for injection. As discussed amply in the specification (page 8, lines 10-15) aztreonam arginine salt is only approved for injection purposes because when administered to the lungs by aerosolization, it causes very undesirable secondary symptoms and complication such as bronchospasm, irritation, inflammation and cough. These undesirable properties were the reason why Applicants, who are in

business of providing drugs for aerosolization for treatment of pulmonary infections, were seeking the new salt and form of aztreonam.

As disclosed on page 8, lines 10-15, of the specification, aztreonam arginine salt is not currently approved for inhalation purposes because the arginine salt is known to cause pulmonary inflammation, bronchospasm, cough and irritation. Any use of the aztreonam arginine for inhalation purposes would thus be contradictory and unsafe. A person skilled in the art would know that aztreonam arginine salt is not useful for inhalation purposes because it is unsafe.

Salts disclosed in Varia are specifically limited to arginine and other, sodium containing salts, such as sodium carbonate, sodium bicarbonate, sodium citrate, sodium phosphate and sodium hydroxide. Specifically, the application identifies α- or β-aztreonam mixed with arginine or another above named salt in dry state and then mixed with water to bring the pH to 5.0.

As disclosed in the current specification, the α-aztreonam lysinate salt is prepared by dissolving, individually, α-aztreonam and lysine monohydrate, in an aqueous solvent and combining both together either adding the lysine to α-aztreonam solution or the aztreonam to the lysine. This reaction yields a substantially pure α-aztreonam lysinate (with impurities levels about 1% or lower) directly without need for any purification.

The Varia reference does not disclose the process for preparation of pure α-aztreonam lysinate, the only form suitable for administration by inhalation, Varia does not address purification of the aztreonam salt required for inhalation purposes in order to prevent bronchospasm during inhalation, does not recognize need and advantages of using α-aztreonam compared to β-

aztreonam for preparation of aztreonam for aerosol, use or preparation of aztreonam as a lysine salt and does not describe or suggest that the α-aztreonam lysinate would have properties that would overcome disadvantages of the arginine salt.

Applicants respectfully point our that their claims concern solely the aztreonam lysinate and that these claims are not obvious from Varia reference. If Varia's aztreonam arginine or other salts were to be used for inhalation, it would cause severe health problems for the recipient.

Examiner further argues that Bastin reference teaches that the selection of an appropriate salt form for a new chemical entity provides the pharmaceutical chemist and formulation scientist with the opportunity to modify the characteristics of the potential drug substance and to permit the development of dosage forms with good bioavailability, stability, manufacturability, and patient compliance. Salts are most commonly employed for modifying aqueous solubility, however the salt form will influence a range of other properties, such as melting point, hygroscopicity, chemical stability, dissolution rate, solution pH, crystal form, and mechanical properties (Abstract).

According to Examiner, Bastin further teaches that drug candidates are usually free bases, free acids, or neutral molecules, rather than their salts (page 427, right hand column, 1st paragraph) and that for weakly basic drug substances, salts of amino acids (arginine or lysine), could be considered (page 428).

Applicants disagree. Bastin reference has been already discussed above. The Bastin publication provides a generic information describing processes used in pharmaceutical industry for formulating new chemical entities. The article does not disclose or suggest anywhere that for an inhalable formulation the

drug must be provided in a safe form that is non-irritating and unsafe to the lungs, and must be water soluble and reasonably stable. Contrary to Examiner's argument, and proving the Applicants point even more, is the fact that Bastin's salts, namely the arginine, histidine and lysine, are lumped into one group of cationic amino acids, thus suggesting that they are freely exchangeable. Clearly, Bastin has no appreciation or understanding of any physiological differences between these salt, and particularly the unsuitability of the arginine salt for inhalation purposes.

That, of course, is contrary to a person skilled in the art knowledge and shows that the Bastin reference is not only irrelevant but its teachings are contrary to what is well known in the art and its combination with Varia makes the obviousness rejection even more unsustainable.

Examiner further rejects the claims over Akehurst reference. Again, the cited reference is not relevant to the current invention and claims. It concerns aerosols suitable for treatment of asthma or other pulmonary diseases that are substantially free of a surfactant. The drug disclosed by Akehurst is salmeterol xinafoate in combination with an anticholinergic agent delivered by propellant tetrafluromethane derivative. The formulation does not concern aztreonam lysinate or alpha aztreonam lysinate, does not teach that the aztreonam lysinate alone when prepared in powder sizes disclosed herein, without any other additional compound, propellant, enhancer or additive can be conveniently delivered to the lungs and that this simple but very specific composition effectively treats the gram-negative bacterial infections that are resistant to other antibiotics.

Applicants respectfully submit that the Akehurst reference,

alone or in combination with Varia and/or Bastin and/or with PLC reference, already discussed above, does not make the current invention obvious and should be withdrawn. It is so respectfully requested.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Claims 12-15, 21-25 and 29-33 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 39-45 and 47 of copending Application No. 10/654,815 (copending '815) in view of Bastin et al.

Although the conflicting claims are not identical, they are not patentably distinct from each other because these claims are

overlapping in scope and/or have the same limitations. The intended uses suggested in claims 39-40 in copending '[815 and in claims 14 and 19 of the instant application have been given no weight, because these are composition claims. Similarly, method steps in composition claims not affecting the composition (e.g. administration) have not been given any weight in the examination.

The claims of the instant application are drawn to alpha-aztreonam (e.g., alpha, beta, delta, etc.).

Claims 41-46 of copending '815 are drawn to pharmaceutically acceptable salts selected form a Markush group that does not include lysinate.

Bastin et al teaches that it is desirable to use salt forms of potential drug candidates, including, for example, salts formed from cationic amino acids such as lysine, arginine, and histidine.

It would have been apparent to a person of ordinary skill at the time of the instant application that a lysinate salt of alpha-aztreonam is obvious over other pharmaceutically acceptable salt forms. A skilled artisan would have been motivated to use the teachings of copending '815 in view of the teachings of Bastion, et al., because the use of salts of pharmaceutical actives is well known in the art. A skilled artisan would also have had a reasonable expectation of successfully using a salt of a known active agent per the art-accepted practices and knowledge regarding salts of drug candidates.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Applicants herein enclose a fully executed Terminal Disclaimed, provisionally disclaiming the terminal portion of the patent over the patent, if such issues, on the application Ser. No.

10/654,815.

Claims 12-15 and 21-29 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 11, 14-17, 20 and 22 of copending Application No. 10/882,985 (copending '985). Although the conflicting claims are not identical, they are not patentably distinct from each other because these claims are overlapping in scope and/or have the same limitations. Both claim sets in the instant application and copending '985 are drawn to compositions comprising powdered aztreonam lysinate, saline or other solutions of aztreonam lysinate, dosages of aztreonam lysinate in solution or powdered form.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Applicants herein enclose a fully executed Terminal Disclaimed, provisionally disclaiming the terminal portion of the patent over the patent, if such issues, on the application Ser. No. 10/882,985.

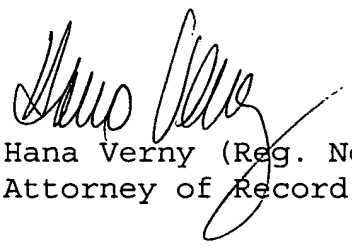
It is respectfully submitted that the double patenting rejection is overcome with submission of these two Terminal Disclaimers.

SUMMARY

In summary, Applicants amended claim 12-15 and 21-31 and provide the arguments to overcome rejections under 35 U.S. C. 103. Two Terminal Disclaimers are submitted to overcome double patenting rejections. With this Amendment and Remarks it is believed that all claims are in conditions for immediate allowance. Notice of Allowance is respectfully solicited.

Should the Examiner require minor changes Examiner is encouraged to call the undersigned at 650-324-1677.

Respectfully submitted,



Hana Verny (Reg. No. 30,518)
Attorney of Record

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PETERS, VERNY, JONES, SCHMITT & ASTON, LLP
425 Sherman Avenue, Suite 230
Palo Alto, CA 94306
TEL 650 324 1677 / FAX 650 324 1678
Atty. Dkt.: 3818.02-5 (HV)
Customer No.: 23308